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Prevalence of human herpesvirus 8 and hepatitis C virus in a rural community with a high risk for blood-borne infections in central China

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Abstract

Illegal blood donation in the past decade has caused human immunodeficiency virus (HIV) outbreaks in some rural areas in China. Other HIV-associated virus infections, such as those caused by human herpesvirus 8 (HHV8), in such areas are still not well defined. In order to explore HHV8 and hepatitis C virus (HCV) seroprevalence and potential risk factors in such areas, a cross-sectional study with 305 HIV-positive and 315 HIV-negative subjects recruited from a rural county in Shanxi province was conducted, in which illegal blood collection was reported. Interview questionnaires and serum testing were carried out with these participants. HCV and HHV8 seroprevalence were found to be higher in the HIV-positive than in the HIV-negative group (76.4% vs. 2.5% and 15.4% vs. 4.8%, respectively), whereas the difference in HBV seroprevalence was not significant. Co-infection with HCV and HHV8 was also more prevalent in the HIV-positive group. HIV status (OR 2.71; 95% CI 1.16–6.30) and HBV status (OR 2.56; 95% CI 1.14–5.75) were independently associated with HHV8 infection. HIV status (OR 23.03; 95% CI 9.95–53.27) and blood/plasma selling history (OR 14.57; 95% CI 7.49–28.23) were strongly associated with HCV infection. These findings demonstrate that both HHV8 and HCV infections are prevalent in this community. HIV infection is an important risk factor for both HHV8 and HCV infection. HBV infection is associated with HHV8 infection but not with HCV infection. It is possible that HHV8 and hepatitis B virus, but not HCV, have similar modes of transmission in this population.

Keywords: HCV, HHV8, HIV, illegal blood donor, seroprevalence
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Introduction

Human herpesvirus 8 (HHV8), also known as Kaposi's sarcoma (KS)-associated herpesvirus, a member of the gamma herpesvirus family, has consistently been found to be associated with all forms of KS. It is also associated with other lymphoproliferative diseases, such as primary effusion B-cell lymphomas and multicentric Castleman's disease [1]. HHV8 infection is not ubiquitous, and the prevalence varies between different populations, but it is commonly found in human immunodeficiency virus (HIV)-positive individuals. HHV8 seroprevalence is generally low to moderate in western countries, ranging from 3% to 23% [2–4]. However, in sub-Saharan Africa, the seroprevalence can be as high as 50% in the general population, and is even higher in the HIV-positive population [5–7]. Data from Asian countries suggest that HHV8 seroprevalence is generally low [8]. Several epidemiological studies have been conducted to study the route of transmission and risk factors involved in the acquisition of HHV-8 infection [9–11]. Although salivary transmission has emerged as one of the major routes of transmission, a recent study conducted in Uganda has clearly demonstrated that transmission via blood transfusion can occur, albeit inefficiently [12].

In addition to HHV8, unmonitored blood transfusion may also increase the risk for acquiring hepatotropic viral infections, such as those caused by hepatitis C virus (HCV) and hepatitis B virus (HBV). These viruses have been known to share routes of transmission and risk factors with HIV. It has also been reported that HCV co-infection is very common among HIV-positive populations [13,14].

During the early 1990s, illegal plasma and blood collection by commercial establishments was common in rural areas of

central China, mainly as a means for rural farmers to augment their household income [15]. Practices such as pooling of blood and re-infusion of red blood cells from donors with compatible blood types exposed the blood donors to various blood-borne pathogens, including HIV. This practice had led to an outbreak of HIV in rural central China. Since the first outbreak of HCV infection among plasma donors in China in 1991, studies have shown a high seroprevalence of HCV in the illegal blood donor population [13,16]. In contrast, very little is known about HHV8 epidemiology in China, especially in this unique high-risk population. A few studies on HHV8 prevalence in mainland China and in Xinjiang Uygur autonomous region in north-western China, which is an endemic area for KS, have been reported [17,18]. No seroprevalence studies of HHV8 have been conducted in areas of central China where large numbers of illegal commercial blood/plasma donors reside, even though high prevalence of HCV and HIV has been observed in this area. The prevalence of HHV8 in this population and its correlation with HIV, HBV and HCV infection is not known.

Therefore, we conducted a cross-sectional epidemiological study to ascertain the seroprevalence of HHV8 and HCV among HIV-infected patients, and compared them with HIV-negative individuals, in a rural area in Shanxi province of central China. To our knowledge, this is the first study to document HHV8 seroprevalence in this population. These findings will contribute to an enhanced awareness of HHV8 infection among these former blood donors.

Materials and Methods

Study cohort and sample collection

The present study was conducted in Yun-cheng city, a rural prefecture area of Shanxi province in central China, a community that harbours a large number of former illegal blood donors. The first case from Yun-cheng city of HIV infection in a plasma donor who had donated for commercial gain was reported in 1996. From then, 626 HIV/AIDS cases had been reported by the end of 2004. Of these, 246 patients had died, and 43 were untraceable.

A total of 620 subjects were included in the present study, and all samples were collected in late 2004 to early 2005 for an observational study on the quality of life in this population. All samples were divided into two groups. The first was the HIV-positive group: All HIV-infected adults were recruited from the local clinic, which offered free antiretroviral treatment as part of the national anti-HIV/AIDS campaign. Only adults participated in this study, and 305 of 326 subjects (93.6%) gave consent. The other 21 patients were unreachable, or refused to be interviewed or provide blood samples. The second group was the HIV-negative group: This group included 315 HIV-uninfected individuals who were randomly selected from a local community-based adult HIV screening programme from a village in the study area.

Venous blood was drawn from each study subject, coded with a unique identification number and then transferred to the laboratory within 4 h of collection. Plasma was aliquoted and stored at −70°C. All assays were performed blindly, and this study was approved by the Institutional Review Board of Fudan University, Shanghai, China.

Serological testing

HIV. All samples were screened with commercial ELISA (Abbott Laboratories, Chicago, IL, USA) for HIV antibodies, according to the manufacturer's protocol. Samples that tested positive by ELISA were confirmed by western blotting.

HCV and HBV. ELISA for HBV surface antigen and anti-HCV IgG antibodies was conducted to determine HBV and HCV infection status, according to the manufacturer's protocol (Wantai Biomedical, Beijing, China). All samples were assayed in duplicate.

HHV8. Plasma samples were tested by monoclonal antibody-enhanced immunofluorescence assay, as reported previously [19]. Briefly, two HHV8 serology tests were used. First, BC-3 cells (an HHV8-positive and Epstein–Barr virus negative B-cell line (American Type Culture Collection, Manassas, VA, USA)), stimulated with tetradecanoyl phorbol acetate, were fixed, permeabilized and used for monoclonal-enhanced immunofluorescence assay. Second, *Spodoptera frugiperda* clone 9, expressing three viral recombinant proteins, ORF73, ORF65 and K8.1, was used for testing. The procedure was similar to the BC-3 immunofluorescence assay. A sample was considered to be HHV-8-seropositive only if it was positive at a standard serum dilution of 1 : 40 with both the BC-3 and the *S. frugiperda* clone 9 assay. Each slide was read independently by two experienced laboratory workers.

Statistical analysis

Original questionnaire data and laboratory results were entered and managed with EpiData 3.0, and then transferred to SPSS v11.5 (SPSS, Chicago, IL, USA) for further analysis. Pearson chi-square test and univariate logistic regression analyses were performed to explore correlates of HCV or HHV8 seropositivity. Multiple logistic regression analyses were conducted to identify risk factors for HCV or HHV8 prevalence after adjusting for potential confounders. ORs with 95% CIs were generated to determine whether a vari-

able was independently associated with HCV or HHV8 prevalence. All p-values ≤0.05 were considered to be statistically significant. The Mann–Whitney *U*-test was used to assess the difference in geometric mean titres (GMTs) of HHV8 between the HIV-positive and HIV-negative groups. All statistical analyses were carried out using SPSS software v11.5. GraphPad Prism 5.0 (GraphPad, La Jolla, CA, USA) was used to construct figures.

Results

Study cohort and characteristics

We enrolled 620 study participants (median age 43.0 years) from Yun-cheng city for the purposes of this study. The Han ethnic group is the major ethnic group in this province. The differences in ethnicity, age group, marital status, education and profession between the two groups were not significant. HIV-positive individuals were more likely to have multiple sex partners and to have never used a condom. Seventy-three per cent of the HIV-positive individuals sold blood/plasma at least once, 16.1% had a history of receiving blood transfusions, and 11.1% had a history of surgery. The major demographic characteristics of all participants (305 HIV-positive and 315 HIV-negative subjects) are summarized in Table 1.

TABLE 1. Characteristics of study participants

	HIV-positive group, no. (%)	HIV-negative group, no. (%)	Total (%)
Gender (p 0.002)			
Male	165 (54.1)	132 (41.9)	297 (47.9)
Female	140 (45.9)	183 (58.1)	323 (52.1)
Ethnicity (p 0.078)			
Han	302 (99.0)	315 (100.0)	617 (99.5)
Others	3 (0.9)	0 (0)	3 (0.5)
Age group (years) (p 0.029)			
19–29	10 (3.3)	18 (5.7)	28 (4.5)
30–49	224 (73.4)	201 (63.8)	425 (68.6)
≥50	71 (23.3)	96 (30.5)	167 (26.9)
Marital status (p 0.720)			
Married	292 (95.7)	302 (95.9)	594 (95.8)
Single	4 (1.3)	6 (1.9)	10 (1.6)
Divorced/widowed	9 (3.0)	7 (2.2)	16 (2.6)
Education (p 0.019)			
Illiterate	26 (8.5)	14 (4.4)	40 (6.5)
Primary school	109 (35.7)	111 (35.3)	220 (35.5)
Middle school	154 (50.5)	156 (49.5)	310 (50.0)
High school or higher	16 (5.2)	34 (10.8)	50 (8.1)
Farmer (p 0.019)			
Yes	290 (95.1)	284 (90.2)	574 (92.6)
No	15 (5.0)	31 (9.1)	46 (7.4)
Multiple sex partners (p 0.012)			
Yes	16 (5.2)	5 (1.6)	21 (3.4)
No	289 (94.8)	310 (98.4)	599 (96.6)
Ever used condoms (p <0.001)			
Yes	256 (83.9)	290 (93.8)	546 (88.9)
No	49 (16.1)	19 (6.0)	68 (11.1)
Ever had blood transfusion (p <0.001)			
Yes	49 (16.1)	16 (5.1)	65 (10.5)
No	256 (83.9)	299 (94.9)	555 (89.5)
Ever donated blood/plasma (p <0.001)			
Yes	223 (73.1)	0 (0)	223 (35.9)
No	82 (26.9)	315 (100)	397 (64.1)
Ever had surgery (p <0.001)			
Yes	34 (11.1)	12 (3.8)	46 (7.5)
No	271 (88.9)	303 (96.2)	574 (92.5)

HHV8 serology and associated risk factors

We conducted logistic regression analysis for risk factors associated with HHV8 seroprevalence in this population. HHV8 seroprevalence was significantly higher in HIV-positive than in HIV-negative individuals (15.4% vs. 4.8%, respectively; p <0.001). The univariate analysis showed that HIV infection, HBV infection and a history of blood/plasma donation were associated with HHV8 infection. Multiple logistic regression analysis indicated that HIV and HBV infection were independently associated with HHV8 infection (OR 2.71, 95% CI 1.16–6.30, and OR 2.56, 95% CI 1.14–5.75, respectively) (Table 2).

HHV8 antibody titre distribution

We also wanted to determine whether the GMT of HHV8 antibodies differed between the HIV-positive and HIV-negative groups. Therefore, plasma from all HHV8-seropositive subjects was serially diluted and tested for IgG anti-HHV8 antibody titre. As shown in Fig. 1, the GMTs of HHV8 antibodies were 417.3 (95% CI 319.5–545.1) for the HIV-positive group (n = 47) and 403.2 (95% CI 294.7–551.6) for the HIV-negative group (n = 15). We did not observe any significant difference in the GMTs of HHV8 antibodies between the HIV-positive group and the HIV-negative group (Mann–Whitney *U*-test = 357.5, p 0.782).

HCV serology and associated risk factors

HCV seroprevalence was significantly higher in the HIV-positive group than in the HIV-negative group (74.4% vs. 2.5%, respectively; p <0.001). In the univariate analysis, gender, condom usage, HIV status, history of selling blood/plasma and history of surgery were found to be associated with HCV infection. Multivariate analysis indicated that subjects who were HIV-positive (OR 23.03; 95% CI 9.95–53.27) and those who had a history of selling blood/plasma (OR 14.57; 95% CI 7.49–28.23) were more likely to be HCV-seropositive than those who were HIV-negative or had no history of selling blood/plasma (Table 3).

Co-infection with HBV, HCV and HHV8

The overall seroprevalence of HBV, HCV and HHV8 among the study subjects was 7.3% (45/620), 38.9% (241/620) and 10.0% (62/620), respectively. The seroprevalence of HBV, HCV and HHV8 was 7.5% (23/305), 76.4% (233/305) and 15.4% (47/305), respectively, in the HIV-positive group, and 7.0% (22/315), 2.5% (8/315) and 4.8% (15/315), respectively, in

TABLE 2. Seroprevalence and correlates of human herpesvirus 8 infection among the study subjects

Characteristics/risk factor	Positive/ Total (%)	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p-Value	OR (95% CI)[a]	p-Value
Gender					
Male	26/297 (8.8)	1.00			
Female	36/323 (11.1)	1.31 (0.77–2.22)	0.323		
Age group (years)					
19–29	2/28 (7.1)	1.00			
30–49	46/425 (10.8)	1.58 (0.36–6.86)	0.543		
≥50	14/167 (8.4)	1.19 (0.26–5.54)	0.825		
Education					
Illiterate	4/40 (10.0)	1.00			
Elementary school	26/220 (11.8)	1.21 (0.40–3.66)	0.741		
Middle school	28/310 (9.0)	0.89 (0.30–2.69)	0.842		
High school or higher	4/50 (8.0)	0.78 (0.18–3.35)	0.741		
Farmer					
Yes	58/574 (10.1)	1.00			
No	4/46 (8.7)	0.85 (0.29–2.45)	0.759		
Ever married					
Yes	61/610 (10.0)	1.00			
No	1/10 (10.0)	1.00 (0.12–8.03)	1.000		
Multiple sex partners					
Yes	2/21 (9.5)	0.95 (0.22–4.16)	0.941		
No	60/599 (10.0)	1.00			
Ever used condoms					
Yes	56/546 (10.3)	1.18 (0.49–2.85)	0.712		
No	6/68 (8.8)	1.00			
HIV infection status					
Positive	47/305 (15.4)	3.64 (1.99–6.67)	<0.001	2.71 (1.16–6.30)	0.021[b]
Negative	15/315 (4.8)	1.00		1.00	
HBsAg					
Positive	9/45 (20.0)	2.46 (1.12–5.39)	0.024	2.56 (1.14–5.75)	0.022[b]
Negative	53/575 (9.2)	1.00		1.00	
Ever had blood transfusion					
Yes	8/65 (12.3)	1.30 (0.59–2.87)	0.513		
No	54/555 (9.7)	1.00			
Ever donated blood/plasma					
Yes	37/223 (16.6)	2.96 (1.73–5.60)	<0.001	1.493 (0.71–3.18)	0.299
No	25/397 (6.3)	1.00		1.00	

HBsAg, hepatitis B virus surface antigen; HIV, human immunodeficiency virus.
[a]OR and p-value were obtained with a multiple logistic regression model, which was adjusted for all demographic variables listed in this table.
[b]p-values ≤0.05 were considered statistically significant.

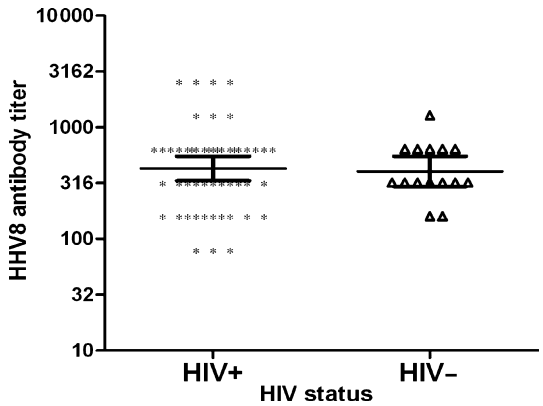

FIG 1. GMT of HHV8 antibodies in seropositive participants in the HIV positive and negative groups. *Antibody titers were determined by IFA based on BC3 slides. GMT for both groups were calculated and compared. (Mann-Whitney U = 357.5, P = 0.782).

the HIV-negative group. The HIV-positive group and the HIV-negative group had no significant difference in the prevalence of HBV (p 0.789), but had significant differences in the prevalence of both HCV (p <0.001) and HHV8 (p <0.001). As shown in Table 4, 54 (17.7%) HIV-positive individuals were not co-infected with HBV, HCV or HHV8. However, 202 (66.2%) were co-infected with either one of the three viruses; 46 (15.1%) were co-infected with two viruses, and three (1.0%) were co-infected with all three viruses. Among the 202 HIV-positive individuals who were co-infected with only one of the above three viruses, 187 (92.6%) were co-infected with HCV (Table 4). Among the 46 HIV-positive individuals with co-infections with two of the three viruses, 31 (67.4%) were co-infected with HCV and HHV8. Among HIV-negative individuals, the majority (87.3%) were negative for all three viruses. Thirty-five (11.1% of 315) were co-infected with only one other virus, of whom 51.4% were HBV-infected. Five (1.6%) were co-infected with two other viruses (HBV, HCV and/or HHV8), and none with all three viruses (Table 4).

Discussion

Given the continuing spread of the HIV/AIDS epidemic in China, HHV8, which causes an important opportunistic

TABLE 3. Seroprevalence and correlates of hepatitis C virus infection among the study subjects

Characteristics/risk factor	Positive/ Total (%)	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p-Value	OR (95% CI)[a]	p-Value
Gender					
Male	142/297 (47.8)	1.00		1.00	
Female	99/323 (30.7)	0.48 (0.35–0.67)	<0.001	0.82 (0.45–1.50)	0.52
Age group (years)					
19–29	7/28 (25.0)	1.00			
30–49	167/425 (39.3)	1.94 (0.81–4.67)	0.138		
≥50	67/167 (40.1)	2.01 (0.81–4.99)	0.133		
Education					
Illiterate	19/40 (47.5)	1.00			
Elementary school	91/220 (41.4)	0.78 (0.40–1.53)	0.471		
Middle school	123/310 (39.7)	0.73 (0.38–1.41)	0.344		
High school or higher	8/50 (16.0)	0.22 (0.08–0.56)	0.002		
Farmer					
Yes	230/574 (40.1)	1.00		1.00	
No	11/46 (23.9)	0.47 (0.23–0.94)	0.034	0.61 (0.17–2.17)	0.45
Ever married					
Yes	237/610 (38.9)	1.00			
No	4/10 (40.0)	1.05 (0.29–3.76)	0.941		
Multiple sex partners					
Yes	10/21 (47.6)	1.45 (0.61–3.46)	0.405		
No	231/599 (38.6)	1.00			
Ever used condoms					
Yes	198/546 (36.3)	0.33 (0.20–0.56)	0.001	0.69 (0.28–1.76)	0.44
No	43/68 (63.2)	1.00		1.00	
HIV infection status					
Positive	233/305 (76.4)	124.19 (58.66–262.91)	<0.001	23.03 (9.95–53.27)	<0.001[b]
Negative	8/315 (2.5)	1.00		1.00	
HBsAg					
Positive	16/45 (35.6)	0.86 (0.46–1.62)	0.636		
Negative	225/575 (39.1)	1.00			
Ever had blood transfusion					
Yes	28/65 (43.1)	1.22 (0.72–2.04)	0.463		
No	213/555 (38.4)	1.00			
Ever donated blood/plasma					
Yes	202/223 (90.2)	88.29 (50.54–154.20)	<0.001	14.57 (7.49–28.23)	<0.001[b]
No	39/397 (9.8)	1.00		1.00	

HBsAg, hepatitis B virus surface antigen; HIV, human immunodeficiency virus.
[a]OR and p-value were obtained by with a multiple logistic regression model, which was adjusted for all demographic variables listed in this table.
[b]p-values ≤0.05 were considered statistically significant.

TABLE 4. Summary of infection by hepatitis B virus (HBV), hepatitis C virus (HCV) and human herpesvirus 8 (HHV8) in the human immunodeficiency virus (HIV)-positive and HIV-negative groups

	HIV-positive group (*N* = 305)		HIV-negative group (*N* = 315)	
Co-infected with:	No.	Prevalence (%)	No.	Prevalence (%)
None	54[a]	17.7	275	87.3
Single virus only				
HBV	5[a]	1.6	18	5.7
HCV	187[a]	61.3	6	1.9
HHV8	10[a]	3.3	11	3.5
Two viruses				
HBV + HCV	12[a]	3.9	1	0.3
HBV + HHV8	3[a]	1.0	3	1.0
HCV + HHV8	31[a]	10.2	1	0.3
Three viruses				
HBV + HCV + HHV8	3[a]	1.0	0	0

[a]These infections are HHV8, HCV or HBV plus HIV.

infection, could become a major public health concern in China. However, little information is available for the prevalence and transmission patterns of HHV8 among the Chinese population, which could be of great importance for HHV8 prevention and control in China and for HIV/AIDS care in particular. Therefore, studies on the modes of HHV8 transmission and risk factors for HHV8 acquisition in China are required.

The results from this study demonstrated a higher HHV8 seroprevalence (15.4%) in the HIV-positive group than in the HIV-negative group (4.8%), which is consistent with other serological studies on the epidemiology of HHV8 infection in Shandong area, a neighbouring province in China [20]. HHV8 prevalence varies considerably between different regions of the country. It is reported to be 19.3–46.6% in the general population of Xinjiang, but only between 7.3% and 16.1% in other provinces in China [17,18,20,21]. In support of other studies conducted in China, we also found that HHV8 infection is not ubiquitous in China. As compared with results from the Xinjiang area, our subjects have a relatively low HHV8 prevalence. These differences may result from ethnicity, socio-economic status, environmental characteristics and hygiene practices. Previous data have shown that both ethnic and socio-economic factors can influence HHV8 infection,

even in the Han population in Xinjiang, which was regarded as a low-risk group throughout China, although the HHV8 prevalence in the same ethnic group is higher than in other parts of China [17]. Interestingly, in our study, the HIV-positive group was found to have a slightly higher anti-HHV8 antibody titre than the HIV-negative group, although the difference was not statistically significant.

As expected, we observed a very high level of co-infection with HCV in the HIV-positive group (76.4%) and a much lower HCV prevalence in the HIV-negative group (2.5%), which reflects the infection rate of the general population in the rest of China. As both HCV and HIV are transmitted via blood, with HCV being more infectious than HIV, it is not surprising that a high HCV co-infection rate was detected in this study. Several studies on HCV co-infection in former blood donors from other areas in China have shown similar results, demonstrating that the HCV prevalence can be as high as 78.6–86.3% among HIV-positive subjects [13,22,23]. Our results further confirm that HCV infection is primarily blood-borne and is of public health importance for antiretroviral therapy in areas with illegal plasma/blood donors.

The current study results suggest that HIV infection is positively associated with both HHV8 and HCV infections. Furthermore, there is an association between HHV8 and HBV co-infection, but not between HHV8 and HCV co-infection. It is possible that factors associated with HBV transmission, such as close familial contact and sharing of hygiene equipment, are also associated with HHV8 transmission. In fact, an association between HHV8 and HBV infection has been reported in previous studies [12,24]. As the HIV transmission route and blood/plasma selling history were independently associated with HCV but not with HHV8 and HBV, it is likely that the HHV8 transmission route in this population is not via blood and is different from that of HCV. The association between HIV and HHV8 co-infection could be attributable to immunosuppression, which rendered HIV-positive individuals more susceptible to HHV8 infection. A previous study on HHV8 transmission has shown that transmission of HHV8 via blood is inefficient [25]. In fact passive transfer of HHV8 antibody was even suggested to have a protective effect against HHV8 transmission [26]. In our study, no association between sexual behaviour, including multiple sex patterns and condom use, and HHV8-positive status was observed. This is also consistent with several previous studies demonstrating that heterosexual transmission of HHV8 is rare [27,28]. Together, these findings support the hypothesis that common routes of transmission are rarely shared by HCV and HHV8 in this area, and this deserves further intensive research.

In conclusion, both HHV8 and HCV infections are prevalent in this former illegal blood-donating community, with HIV acting as an important factor in co-infection. Our data demonstrate that HBV infection is associated with HHV8 infection but not with HCV infection. HHV8 and HBV, but not HCV, may have similar modes of transmission in this population. A number of studies have shown that HHV8 can be detected and potentially be transmitted via saliva contact [29,30], and it is possible that saliva plays an important role in transmission in this study population. We are unable to delineate this route, as saliva samples were not collected as a part of this study. Further, prospective studies on HHV8 seroprevalence and more extensive risk factor analysis, such as living arrangements, hygiene conditions and food-sharing practices, are needed to explore the epidemiology of HHV8 infection in this population.

Transparency Declaration

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